REMARKS

Upon entry of the above amendment, claims 1-6 and 10-31 will be pending, claims 7-9 having been canceled and new claims 25-31 added. Claims 12-24 are withdrawn as being drawn to non-elected inventions. Claims 1-6, 10, 11, and 25-31 are under examination.

Applicants have amended claim 1 to incorporate the language "cell that (i) is infected with a budding virus that comprises a gene encoding a transporter and (ii) is recombinantly expressing the transporter" and "harvesting the released virus, wherein the transporter on the envelope of the released virus has transporter activity." Support for these amendments can be found throughout the specification, e.g., at page 11, lines 18-27; page 12, lines 1-18; and page 30, lines 16-27. The preamble of claim 1 is amended to make it consistent with the claim as a whole. Claim 2 is amended to clarify antecedent basis. Claim 3 is amended for clarity, using a term derived from claim 7 as filed. Claim 5 now spells out the full names of the transporters; these names are understood in the art to correspond to the acronyms in claim 5 as filed, and can be found, e.g., at the sources cited in the specification at page 9, lines 5-11. Support for the limitation added to claim 6 regarding a purified baculovirus is supported, e.g., in original claim 9 (now canceled) and in the specification at page 12, lines 15-18, and page 30, lines 16-27. The new limitation regarding a "mammalian" transporter is supported by the extensive list of transporters provided in Table 1 of the specification at pages 6-9; all of the listed transporters are mammalian transporters. Claims 10 and 11 are amended to be consistent with claim 6. Support for new claims 25 and 26 can be found, e.g., at page 10, lines 35-37. Support for new claims 27-30 can be found, e.g., at page 4, lines 24-37. New claim 31 is supported, e.g., in claim 1 as originally filed. No new matter has been added.

Election/Restrictions

The Restriction Requirement mailed January 25, 2007, restricted the claims into three groups based entirely on an assumption that a prior art reference, Hsu et al., anticipated claim 1 and thus the claims lack "a single inventive concept." Applicants pointed out in their response (with traverse) filed March 5, 2006, that Hsu et al. did not anticipate any of the claims. In the

present Office action, the Examiner addresses Applicants' traversal of the restriction requirement in a sentence that begins with the clause: "While Hsu et al partially meets the limitations of claim 1...." Applicants read that clause as implicitly acknowledging that Applicants' position regarding Hsu et al. is correct (since "partially meets the limitations of claim 1" implies that there is no anticipation). However, the Examiner goes on to reassert his position that the claims lack a single inventive concept, alleging that "...several prior art references meet the limitations disclosed in claim 1." Only one of the alleged "several prior art references that meet the limitations disclosed in claim 1" is identified: Garcia et al., J. Biol. Chem. 270:1843-1849 (1995). Curiously, although the statements at page 2 of the Office action suggest the Examiner believes that Garcia et al. and "several" other references anticipate claim 1 (since anticipation seems to be what he means by "meets the limitations disclosed in claim 1"), only one reference was cited at pages 11-12 of the Office action as anticipating any of the claims, and it was not Garcia et al. If the Examiner believes that Garcia et al. and "several" other references truly anticipate claim 1, that should be set forth as a proper rejection under 35 USC §102, identifying each and every reference that purportedly anticipates and explaining where the limitations of the claims are found in each reference, so that Applicants can understand and directly address the Examiner's reasoning regarding each and every reference. If the Examiner does not believe that Garcia et al. and "several" other references anticipate the claims, then the insinuation at page 2 should be repudiated unambiguously on the record and the finding of lack of unity withdrawn. Meanwhile, Applicants are left in the unenviable position of having to address an anticipation rejection that was implied but never asserted, and without even knowing the identity or content of the "several" references (other than Garcia et al. and the one cited in the rejection under §102, Miyasaka et al.) the Examiner had in mind.

In the context of justifying the restriction of the claims into three groups, the Examiner now says that Garcia et al.

> teach a method of expressing the monocarboxylate transporter having monocarboxylate transporter activity, wherein the method comprises culturing the Sf9 host cells infected with the budding baculovirus virus...Thus Group I lacks novelty or inventive steps and does not make a contribution over prior art.

The above-quoted assertion ignores the limitation of claim 1 (present in original claim 1 as well as claim 1 as presently amended) specifying "expressing the transporter on the envelope of a budding virus released from the host cell." There is no indication in Garcia et al. that the cultured Sf9 host cells released a budding virus having an envelope on which the transporter is expressed, much less that the transporter on the viral envelope possessed transporter activity. Garcia et al. studied transporters expressed on the surface of the cells, not the viral envelope. Furthermore, claim 1 as presently amended requires a further step of harvesting the released virus, a step that Garcia et al. did not carry out and gave no reason to carry out, since the authors were interested solely in studying the activity of the transporter on the cell surface.

Applicants cannot even begin to address the above-quoted remark regarding "inventive steps," as the Examiner provides no clue as to his thinking in this regard.

Withdrawal of the finding that the claims lack unity of invention, novelty and inventive step; examination of all of the presently pending claims; and acknowledgement that Garcia et al. does not "meet the limitations" of claim 1 are respectfully requested. If the Examiner intends to maintain any of these findings, applicants request that a fuller record be provided in another non-final Office action so that applicants have a fair opportunity to respond.

Specification

The title of the invention was objected to as not being descriptive at page 3 of the Office Action mailed May 16, 2007, herein the "Office Action." Applicants have amended the title to read "Expressing Transporters on Viral Envelopes". Withdrawal of the objection is requested.

Claim Objections

At page 3 of the Office Action, claims 5 and 11 were objected to for using acronyms without first defining what the acronyms represent. Claim 5 is amended to define each acronym used in claims 5 and 11. Withdrawal of the objection is therefore requested..

Rejections under 35 U.S.C. § 112, paragraph one (Written Description)

Claims 1-11 have been rejected as failing to comply with the written description requirement. According to the Office Action at page 4, "the specification does not clearly define a transporter having transporter activity, a recombinant virus, a gene encoding the transporter, a budding virus, a transporter of non-viral origin, a peptide transporter, and organic anion transporter analogues, fragments and mutants of [PepT1], PepT2, and OATPC and all methods of using such. The rejection is moot as to claims 7-9, which have been canceled. Applicants traverse with respect to the remaining claims.

According to MPEP § 2163.02,

> Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention...
>
> Possession may be shown in a variety of ways including description of an actual reduction to practice...

The specification amply demonstrates reduction to practice of the invention using all of the following: a transporter having transporter activity, a recombinant virus, a budding virus, a transporter of non-viral origin, a peptide transporter and an organic anion transporter. These terms, and many specific examples of each, were either described in the specification, known in the art at the time of filing, or both. According to MPEP § 2163 II 3(a),

> [t]he description need only describe in detail that which is new or not conventional. See *Hybritech v. Monoclonal Antibodies*, 802 F.2d at 1384, 231 USPQ at 94; *Fonar Corp. v. General Electric Co.*, 107 F.3d at 1549, 41 USPQ2d at 1805 (source code description not required). This is equally true whether the claimed invention is directed to a product or a process. *Emphasis added.*

Use of a transporter having transporter activity, a recombinant virus, a budding virus, a transporter of non-viral origin, a peptide transporter and an organic anion transporter was exemplified in the specification by the isolation of baculovirus, a known budding virus, expressing a transporter having transporter activity, PepT1, PepT2, or OATP-C, on its viral envelope by infecting host insect cells with recombinant baculovirus, a recombinant virus.

Methods for generating recombinant virus are routine. At the time of filing, PepT1 and PepT2 were known peptide transporters (abstract enclosed) and OATP-C was a known organic anion transporter (abstract enclosed). Many other examples of such transporters are listed in Table 1 on pages 6-9 of the specification, all of which are of non-viral origin. The specification provides ample support for the genus "transporter having transporter activity". Given the description in the specification, the skilled practitioner would recognize that a "transporter having transporter activity" is a protein that transports substances across biological membranes. The specification at page 1, lines 16-28, says:

> Mammals must take in nutrients from outside the body, and many transporter proteins (transporters) are known to exist in mammalian cells. These transporters mainly act to transport substances essential to the maintenance of life (amino acids, sugars, and such) into cells.

The specification describes numerous examples of transporters known in the art at table 1, citing references (furthest column to the right) and providing sequence accession numbers (2nd column from right). Thus, even though the written description requirement does not require that transporters known in the art be recited and described in the specification, applicants have done so.

Finally, the Office Action at page 4, alleges that "organic anion transporter analogues, fragments and mutants of PepT1, PepT2, and OATP-C and all methods of using such" suffer from a lack of written description. Applicants are not claiming "analogues, fragments and mutants", nor "all methods of using such". The present claims are drawn to an isolated baculovirus, the envelope of which comprises a transporter having transporter activity, and to methods of expressing a transporter on a budding viral envelope. While active analogues, fragments and mutants of transporters might be employed, they are not essential and need not be described in detail in the specification in order to demonstrate that applicants were in possession of the claimed invention as a whole. The Federal Circuit has made it clear in a number of recent biotechnology patent cases that the written description requirement does not require the sort of exhaustive detail the Office appears to believe would be required in the present case. See, for example, *Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005), *Invitrogen Corporation v. Clontech*

Laboratories, 429 F.3d 1052 (Fed. Cir. 2005), *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006), and *Monsanto Company v. Scruggs*, 459 F.3d 1328 (Fed. Cir. 2006).

For at least these reasons, applicants request the rejection for lack of written description be withdrawn.

Rejections under 35 U.S.C. § 112, Paragraph one (Enablement)

The Examiner, at page 6 of the Office Action, has recognized that the specification is enabling for expression of wild type and His-tagged PepT1 and PepT2 and wild type and mutant N130D, V147S OATP-C in baculovirus; and inhibiting PepT1 activity expressing viruses by anti-human PepT1 monoclonal antibody. However, claims 1-11 stand rejected under the premise that the specification is not enabling for the full scope of the claims. Claims 7-9 are canceled by the above amendment, so the rejection is moot as to them. Applicants traverse this rejection with respect to the remaining claims.

The enablement rejection is made on the grounds that in view of the Wands factors (*In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404), a skilled practitioner would have to perform undue experimentation to carry out the full scope of claims that recite the genus "transporter having transporter activity". Applicants submit that given the information provided in the specification, the genus is fully enabled in view of the Wands factors.

Nature of the invention and breadth of the claims

According to the Office Action at page 7, "[t]he invention is broad because the recitation of claim 1, encompasses a large number of transporter genes, viruses, transporters, and transporter activities." Applicants agree that the claims are broad with respect to those aspects. However, as discussed below, applicants do not agree that the claims are broader than their enabling disclosure.

Unpredictability and state of the art

The Office suggested that the state of the art calls into question whether any transporter expressed on the envelope of a budding virus would retain activity and that the ability to express a functional transporter would be transporter-specific. According to the Office Action at pages 7 and 8,

> The method for each individual transporter must be specifically optimized for that transporter because in some instances the expressed transporter may not have any activities. For instance, Loisel et al. (1997, Nature Biotechnology, Volume 15, pages 1300-1304, cited in the IDS mailed March 09, 2005 as reference BF) recite that the baculovirus/insect cell system offers the advantage of usually high levels of expression of proteins. But a major caveat of the insect cell system is the expression of an important proportion of inactive receptors. As a consequence, receptor purification schemes that do not include a step based on the biological activity of the receptor, such as ligand affinity chromatography, yield heterogeneous preparations contaminated with nonfunctional and possibly misfolded receptors, which may bias physicochemical and structural studies (page 1300, left column, 1st column).

Applicants respectfully traverse. The Examiner has cited Loisel et al. in alleging that a method for expressing an active transporter on the envelope of a budding virus is unpredictable. However, the portion of Loisel et al. cited discusses problems in expressing receptors in cells, not problems in expressing receptors on the envelope of a budding virus. According to Loisel et al. at page 1300, left column, 1st paragraph,

> [i]n several studies, cloned receptors have been found to occur in immature and/or incompletely glycosylated forms in crude cell membrane fractions (CCMF). These forms most likely represent receptors trapped in the endoplasmic reticulum or Golgi apparatus as a result of saturation of the biosynthetic pathway.

Loisel et al. teach that researchers have tried to express and recover heterologous receptor proteins using baculovirus expression in cells, but that receptor proteins contained in crude cell membrane fractions included inactive receptors. Crude cell membrane fractions contain not only components of the cell membrane, but also components of endoplasmic reticulum membranes and Golgi apparatus membranes. Thus, Loisel et al. attribute the presence of inactive receptors in crude cell membrane fractions to contamination with immature forms present in protein

secretory pathways "as a result of saturation of the biosynthetic pathway," (page 1300, 1st column, 1st paragraph). Loisel et al. does not suggest that the envelopes of budding virus would contain such immature forms of receptors, and indeed there would be no reason to expect they would, since the viral envelopes are not derived from the endoplasmic reticulum or Golgi apparatus.

Accordingly, Loisel et al. does not support the Examiner's thesis.

The amount of direction or guidance present

According to the Office Action at pages 8 and 9,

> Applicants' disclosure is limited to expressing wild type and his tag added PepTI and PeptT2 with baculovirus (Figures 1-2), (2) wild type and mutant N130D, V147S OATP-C with a baculovirus (Figure 3), (3) inhibiting PepTI activity expressing viruses by anti-human PepTI monoclonal antibody (Figure 4). However, the specification does not provide guidance or direction regarding a method for expressing other transporters, such as the ones listed in Table 1 (pages 6-9) or Table 2 (pages 23-28), other virus besides baculovirus, or other OATP-C mutants besides the N130D and V147S.

Applicants disagree. It is not clear why the Examiner believes applicants' disclosure is "limited to" the working examples mentioned in the above-quoted text. Applicants' disclosure obviously includes a lot more than that, including the list of transporters and their characteristics in Table 1 and the guidance on how to express them found throughout the specification.

As acknowledged by the Examiner, Table 1 provides numerous examples of transporters. These can be tested by the skilled practitioner using routine procedures given the direction and guidance provided by the specification. As described in the specification at page 9, line 15, to page 10, line 12,

> Genes encoding the transporters, for example, those listed in Table 1, are registered with the National Centre for Biotechnology Information (NCBI) under the listed accession numbers. For example, based on this sequence information, cDNA libraries or genomic libraries can be screened to obtain genes coding for transporters. More specifically, for example, cDNA or genomic libraries are screened using probes (antibodies against target transporters, or oligonucleotides that hybridise to nucleotide sequences coding for target transporters). Screening can be carried out, for example, by following the standard methods described by

> Sambrook et al. in Chapters 10 to 12 of "Molecular Cloning: A Laboratory Manual" (New York, Cold Spring Harbor Laboratory Press, 1989). Alternatively, genes encoding target transporters can be isolated using PCR (see e.g., Chapter 14 in the above-mentioned Sambrook et al., 1989).

The Examiner does not explain why he believes this guidance is not sufficient for one of ordinary skill desiring to use any of the transporters listed in Table 1, or any other transporter known in the art. Following identification of a transporter gene clone, the skilled practitioner could, if she deems it desirable, generate mutant transporters using methods well known in the art and described in the specification at page 21, line 36, to page 22, line 11:

> In addition, after mutants have been created by artificial substitution, insertion, deletion, or addition of transporter amino acid sequences, transporter activity can be measured and transporters with high activity can be screened, or regions that influence transporter activity can be identified. Those skilled in the art can prepare transporters with substituted amino acids by using well-known methods. For example, site-specific mutagenesis and such can be used (Hashimoto-Gotoh, T. et al., Gene, 152, 271-275, (1995); Zoller, M J, and Smith , M., Methods Enzymol, 100, 468-500, (1983); Kramer, W et al., Nucleic Acids Res, 12, 9441-9456, (1984); Kramer, W and Fritz, HJ., Method Enzymol, 154, 350-367, (1987); Kunkel, TA., Proc Natl Acad Sci USA, 82, 488-492, (1985); Kunkel, TA., Methods Enzymol, 85, 2763-2766, (1988)).

Using the transporter gene clone or mutants thereof, the skilled practitioner could produce a recombinant budding virus encoding the transporter using methods described in the specification at page 31, lines 20-33:

> The full-length PepT2 gene was isolated from a human kidney library. PCR was used to integrate the gene encoding the full-length human PepT2 into pBlueBacHis2A (Invitrogen), and a full-length PepT2 transfer vector (pBlueBac) was constructed. This vector was introduced into Sf-9 cells along with the viral DNA. After cloning the recombinant virus constructed by homologous recombination, a stock with a high recombinant virus activity was constructed. Sf-9 cells were infected with the stock virus, and after culturing for a certain period, PepT2 was expressed in the virus and on the membrane of Sf-P cells. PepT2 expression in the virus and on the membrane of the Sf-9 cells was confirmed by Western analysis using anti-His antibodies. More specifically, except for using the PepT2 gene, operations were carried out according to the methods described in Example 1.

Again, the Examiner does not explain why the disclosed techniques cannot be applied to any transporter and any budding virus known in the art.

Having obtained a recombinant virus, the skilled practitioner could infect host cells and recover purified virus expressing the transporter as described in the specification at page 30, lines 16-30:

> Construction of budding-type viruses that express human PepT1 was carried out as follows. Specifically, 500 mL of Sf9 cells (2x 106/mL) were infected with the recombinant viruses prepared as above, so as to achieve MOI=5. After culturing at 27°C for three days, the culture supernatant was centrifuged for 15 minutes at 800x g, and the cells and cell debris were removed. The supernatant recovered by centrifugation was centrifuged at 45,000x g for 30 minutes, and the precipitate was then suspended in PBS. The cellular components were removed by centrifuging for another 15 minutes at 800x g. The supernatant was again centrifuged at 45,000x g for 30 minutes, and the precipitate was again suspended in PBS. This suspension was the budding virus fraction. Expression of PepT1 in the virus and on the Sf-9 cell membrane was confirmed by Western analysis using anti-His antibodies. In addition, protein concentration was measured using Dc Protein Assay kit (Bio-Rad), with BSA as the standard.

Support for alternative budding viruses can be found in the specification at page 11, lines 27-33:

> In addition, using methods like that of Strehlow et al. (D. Strehlow et al., Proc. Natl. Acad. Sci. USA. 97: 4209-4214 (2000)), packaging cells such as PA317 can be infected with recombinant Moloney murine leukemia viruses, which are constructed using vectors derived from Moloney viruses introduced with transporter-encoding genes, and the transporters can be expressed on the envelope of the viruses released outside of the cells.

The Examiner does not explain why he believes one of ordinary skill would not be able to utilize these known viruses and cells in the claimed methods. Given the ample direction and guidance provided by the specification, expressing a "transporter having transporter activity" on the viral envelope of a budding virus would not require undue experimentation. The Examiner has provided no evidence to the contrary.

Working examples

The Office Action notes that applicants have provided a number of working examples. Accordingly, this Wands factor is certainly in applicants' favor. Rather than acknowledge this, the Examiner appears to take the position that it is necessary to provide a working example regarding every known transporter in order to satisfy the enablement requirement (see the statement in the Office Action at page 9: "the specification does not provide any methods or working examples [of] a method for expressing other transporters, such as the ones listed in Table 1..."). Obviously, this is not the proper standard. Given the direction and guidance provided in the specification as described previously, the skilled practitioner could express any number of transporters in Table 1 using the routine procedures disclosed by the specification. The Examiner has suggested no reason to believe otherwise.

The quantity of experimentation needed

According to the Office Action at page 9,

> Without sufficient disclosure in the specification, it would require undue experimentation for one of skill in the art to express a transporter having transporter activity, wherein the method comprises culturing a host infected with a recombinant virus that comprises a gene encoding the transporter, and expressing the transporter on the envelope of a budding virus released from the host. In addition, it would require undue experimentation to practice the invention commensurate in scope with the claims because, the claims are broadly drawn to a method for expressing a transporter having transporter activity, wherein the method comprises culturing a host infected with a recombinant virus that comprises a gene encoding the transporter, and expressing the transporter on the envelope of a budding virus released from the host. Undue experimentation would also be required of the skilled artisan to identify a transporter activity and generate the infinite number of transporter analogs and derivatives recited in the claims and screen same for activity.

The Examiner gives no rationale as to why he believes any of the recited techniques would require "undue experimentation". He simply deems it so. Applicants remind the Examiner that the *In re Wands* court found that, even though considerable experimental work might be required to obtain the few desired antibodies falling within the scope of the claims, the

necessary experimentation was not undue, given that generating and screening monoclonal antibodies was regarded as routine procedure.

As described previously above, the skilled practitioner could use standard techniques to identify a transporter-encoding nucleic acid, clone that nucleic acid into a recombinant baculovirus using a commercial kit, and use that baculovirus to infect host cells under conditions described in the specification. The skilled practitioner could isolate virus expressing a transporter, e.g., by high-speed centrifugation, and then test transporter activity by using radiolabeled substrate (substrate specificity of numerous transporters is given in Table 1). Methods of determining transporter activity are described in the specification at page 30, line 33, to page 31, line 12:

> ^{14}C glycylsarcosine was diluted with HBSS (pH6.0) to a final concentration of 50 μM, and used as a substrate solution. 40 μL of viral solution (100 μg protein) was preincubated at 37°C for 30 minutes. 160 μL of substrate solution that had been preheated to 37°C was added, and the reaction was started. After one minute, 1 mL of ice-cold HBSS (pH 7.4)(hereinbelow also called "quenching solution") was added, and the reaction was stopped. The virus-comprising reaction solution was immediately vacuum filtered using a mixed cellulose membrane filter, and washed twice with 5 mL of the quenching solution. The membrane filter was transferred to a liquid scintillation vial, 5 mL of clear-zol I was added, and the filter was dissolved. After the dissolving, a liquid scintillation counter was used to measure radioactivity on the filter. Non-specific adsorption to the filter was measured in the same way for systems where the quenching solution was added before adding the substrate solution to the viral solution, and values thus obtained were subtracted from the counts for each experiment.

None of this is "undue," given the detailed teachings in the specification combined with the expertise of one of ordinary skill. Thus, in view of the *Wands* factors, and at least for the reasons given above, applicants respectfully request that the enablement rejection be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

The Office Action at page 10 rejected claims 1-11, alleging that the claims are indefinite for two reasons. First, the Office Action opined that "[t]he phrase 'culturing a host' in claim 1 is a relative term which renders the claims indefinite." Applicants traverse. Culturing a host (now

worded in claim 1 "culturing a host cell") is a very standard term easily understood by one of ordinary skill. It is not a "relative term," as alleged by the Office Action without explanation, and it is difficult to see why the Examiner believes otherwise. Biologists routinely "culture" host cells. See, for example, the first paragraph of "Experimental Protocol" on page 1303, col. 2, of Loisel et al.: "Sf9 cells were cultured...". The claim is not limited to specific culture conditions and should not be, as any suitable conditions can be used. One of ordinary skill in the art would know exactly what is encompassed by the term.

Second, the Office alleged that "[t]he phrase 'transporter activity' in claims 1 and 6 is a relative term which renders the claims indefinite." Applicants traverse. Proteins that possess transporter activity are well known in the art. Table 1 lists many known transporters and describes what they do; furthermore, the reference cited for each provides more detailed information. The specification at page 12, line 19, through page 13, line 28, explains how to detect transporter activity in general. Withdrawal of the rejection as unwarranted is requested.

Rejections under 35 U.S.C. § 102(b)

The Office rejected claims 1-4 and 6-10 as being anticipated by Miyasaka et al. According to the Office Action at pages 11 and 12,

> Miyasaka et al. teach a method of expressing the peptide taurine transporter wherein the method comprises culturing Sf9 cells with the recombinant virus baculovirus that comprises the taurine transporter gene and expressing the transporter of a budding virus released from the cell (page 389, abstract) meeting the limitations of claims 1, 2, 8, and 9. It is noted that the budding is an inherent property of the baculovirus.
>
> The mammal taurine transporter is derived from a non-virus and is a peptide transporter encompassing the limitations of claims 3, 4, 7, and 10. Moreover, Miyasaka et al. teach that the virus has taurine transporter activity (figure 3 page 392) meeting the limitations claim 6.

Claims 7-9 are canceled by the above amendment, so the rejection is moot as to them. Applicants submit that the remaining claims are not anticipated by Miyasaka et al., for at least the reasons discussed below.

The Office action appears to be confusing (1) expression of proteins on infected cells, with (2) expression of proteins on the envelope of a budding virus. The mere fact that a given reference discloses use of a baculovirus as a vector for introducing a recombinant gene into a cell does not mean that the reference also discloses expression of the recombinant protein on the virus' envelope. These are of course very different things. Miyasaka et al. employed baculovirus as an expression vector to express the human taurine transporter in Sf9 cells. As explained at page 391, first paragraph, cells were infected with the recombinant baculovirus and cultured, producing cells that expressed the taurine transporter on their surface. The cells were then washed (a step that would remove any released virus) and incubated in a buffer containing labeled taurine, in order to study the uptake of taurine by the cells. The first paragraph of the Results section on page 392 also makes it clear that Miyasaka et al. were studying the activity of the taurine transporter expressed on the cells (not on the virus). Miyasaka et al. did not harvest the baculovirus produced by the cells, as required by amended claim 1, and did not examine what proteins may or may not have been present on the envelope of the baculovirus, much less characterize their activity. They certainly did not "teach that the virus has taurine transporter activity," as asserted by the Office action at page 12. The Office action refers to FIG.3 of Miyasaka et al. to support the rejection; however, both FIG.3 and FIG.2 of Miyasaka et al. concern taurine uptake by the infected cells, not by baculovirus released by the cells. The activity of a recombinant transporter expressed on cells is irrelevant to the present claims. Thus, Miyasaka et al. does not teach all of the limitations of claim 1.

Claim 6 has been amended to specify that the virus is "purified." Miyasaka et al. does not teach anything about the envelope of a baculovirus and does not teach purification of a baculovirus the envelope of which comprises a mammalian transporter having transporter activity. To the contrary, Miyasaka et al. discarded whatever virus may have been produced by their infected cells without characterizing the viral envelope at all, as they were interested in studying the transporter as expressed on the cells.

Applicants point out that new claims 27-30 depend from claim 1 and specify other limitations that further distinguish over Miyasaka et al. Claim 27 requires assaying the harvested

virus for activity of the transporter, and claim 28 requires confirmation of the activity. Claims 29 and 30 recite using the harvested virus in an assay for detecting whether a test compound is transported by the transporter or inhibits the activity of the transporter, respectively. None of these actions are disclosed by Miyasaka et al.

For at least these reasons, applicants request that the rejection be withdrawn as to all of the pending claims.

Applicants again note that the Office action at page 2 inexplicably states that "Group I lacks novelty" in view of Garcia et al. and "several" other prior art references that the Examiner neglected to identify, yet does not reject the claims as anticipated by Garcia et al. or any other reference other than Miyasaka et al. It is unclear whether the Examiner intended to reject some or all of the claims as anticipated under §102 in view of Garcia et al., and if so, why that rejection was not made explicit, rather than couching the observation merely in terms of lack of unity in another section of the Office action. Despite these issues, applicants, in the interest of moving prosecution along efficiently, have attempted to address the nonexistent rejection over Garcia et al. in the above discussion regarding lack of unity. It is not repeated here. Even more troubling is the allegation on page 2 that the claims lack novelty in view of "several" prior art references the Examiner chose not to reveal. Applicants are at a loss as to how to respond to that allegation. ***If the Examiner intends to assert any allegedly anticipatory prior art other than Miyasaka et al. against the claims, it will have to be properly done in a non-final Office action that identifies the prior art and the reasons for rejection, so that applicants have a fair opportunity to respond.***

Rejections under 35 U.S.C. § 103(a)

The Office Action at page 12 rejected claims 5 and 11 as obvious over Miyasaka et al., further in view of Hsu et al. (Pharmaceutical Research, 15: 1376-1380, 1998). According to the Office Action at pages 12-13,

> [I]t would be obvious for one skilled in the art to modify the method for expressing a transporter having transporter activity, wherein the method comprises culturing a host infected cell with a recombinant virus that comprises a

gene encoding the transporter, expressing the transporter on the envelope of a budding virus released from the host as taught by Miyasaka et al. (2001, protein expression volume 23, pages 389-397) by using the transporter, PepT1, as taught by Hsu et al. (1996). One of ordinary skill in the art at the time the invention was made would been motivated to express Pept1 in baculovirus because gene delivery using a variety of viral and synthetic vectors provides a novel strategy for treating diseases and delivery of therapeutic proteins (Hsu et al., page 1376, right column, 2nd paragraph). One skilled in the art would have expected success because the PepT1 gene has been expressed successfully in a viral vector and numerous other membrane transporters have already been expressed in Sf9 cells using the baculovirus system at the time the invention was made. Accordingly, the invention taken as a whole is prima facie obvious.

Again, the Office action appears to be confusing (1) expression of proteins in infected cells, with (2) expression of proteins on the envelope of a budding virus. The mere fact that a given reference discloses use of a baculovirus as a vector for introducing a recombinant gene into a cell does not mean that the reference also discloses expression of the recombinant protein on the virus' envelope. As stated above, these are very different things. Applicants reiterate that Miyasaka et al. teach methods for expressing recombinant taurine transporter in insect cells in order to study transporter activity in cells, not on the envelopes of virus released from the cells. Miyasaka et al. do not teach or suggest a step of harvesting or otherwise purifying a budding virus from the infected cells, and provide no reason one might want to do so. Quite the contrary: Miyasaka et al. teach washing the cells to prepare them for taurine uptake studies, in the process discarding whatever virus may have been shed. Thus, if anything, Miyasaka et al. *teach away* from a method that requires harvesting the virus. Further, Miyasaka et al. do not suggest that the envelopes of viruses released by the infected cells might contain the transporter protein, much less suggest that the transporter on the viral envelope might have transporter activity (as required by the present claims even prior to amendment). Miyasaka et al. are entirely silent on these points.

Hsu et al. is cited for its disclosure of a recombinant adenovirus encoding PeptT1, so does not make up for the deficiencies of Miyasaka et al. in this regard. Adenoviruses, of course, are not enveloped viruses.

It is clear from above that the Examiner has not shown where all of the limitations of claim 1 or claim 6, or any claims that depend therefrom, can be found in the art. Nor has the Examiner identified a reason one of ordinary skill in the art might have relied upon to alter the teachings of the cited references in order to come up with the presently claimed inventions. Furthermore, the Examiner has not established that one of ordinary skill in the art would have expected that the invention would work, i.e., that the viral envelope of a budding virus such as a baculovirus could be made to express a transporter having transporter activity. Applicants submit that, prior to applicants' work, one could not have predicted success in that regard. Miyasaka et al. didn't study that question, so provides no guidance, and Hsu et al. didn't utilize an enveloped virus at all, so is irrelevant. As elaborated below, two other references, Marheineke et al. (FEBS Lett., 441:49-52, 1998, reference AE on the Form PTO-1449 submitted herewith) and Braunagel et al. (Virology, 202:315-328, 1994, reference AC on the Form PTO-1449 submitted herewith) suggest that the composition of the host cell's membrane was known to differ from that of the envelope of a virus budding from that host cell.

Marheineke et al. analyzed the phospholipid composition of the plasma membrane of Sf9 cells. They teach that, while phosphatidylethanolamine, phosphatidylcholine, and phosphatidylinositol are major components of the Sf9 plasma membrane, phosphatidylserine could not be detected (page 50, col. 1). In marked contrast, Braunagel et al. found that phosphatidylserine is the major phospholipid component (about 50% of total phospholipids) of the extracellular baculovirus envelope (page 322, col. 2, lines 1-2, and Table 1). Marheineke et al. further state at page 51, col. 1, 1st full paragraph, that in general the activity of functional membrane proteins is likely to be influenced by the properties of the lipid bilayer:

> In analogy to the dependence of soluble enzymes on the composition and characteristics of their aqueous milieus the activity of functional membrane proteins is influenced by the properties of the lipid bilayer.

Thus, the art had no expectation that a functional recombinant transporter could be expressed on a budding viral envelope just because it can be found on an Sf9 cell membrane.

For at least these reasons, applicants submit that the Examiner has not made out a *prima facie* case of obviousness, and request that the obviousness rejection be withdrawn.

The fees in the amount of $200 for the excess claims fee, $180 for submission of an Information Disclosure Statement and $1050 for the Petition for Three Month Extension of Time Fee are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-133US1.

Respectfully submitted,

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